THE PROBLEMS OF PHOTOSENSITIVITY[1]

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The purpose of this paper is:

1. To define photosensitivity and photosensitizers.
2. To state the results of photosensitivity.
3. To discuss the mechanism of photosensitivity.
4. To indicate briefly specific conditions allied to photosensitivity.
5. To discuss the management of the problem
   (a) By medical means (briefly only),
   (b) By physical means with which the physiotherapist may be involved including:
      (i) spectrophotometry;
      (ii) results of experiments with filters and sun, and physical screens.
6. To describe experiments performed to check the properties of accepted sensitizers and desensitizers.

I am assuming photosensitivity to mean any abnormal changes which can occur as a result of exposure to light, either sunlight, ultra violet or even the rays present in standard indoor fluorescent lighting. The agent or photosensitizer is any drug or substance which is suspected of inducing the reactions observed.[1]

These reactions are divided into two groups:

(a) Phototoxic reactions;

(b) Photoallergic reactions.

Phototoxic Reactions

If a reaction occurs frequently and is evoked by the erythema producing spectrum in shorter than average time and with less than usual exposure, it is said to be a phototoxic reaction.[2]

Photoallergic Reaction

This reaction requires by definition previous exposure and sufficient time to lapse to allow the individual to develop a state of altered reactivity.[3]

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The number of individuals involved in the photoallergic reaction is smaller than those in the phototoxic group. The amount of exposure necessary to evoke the response is reported to be greater and also the response is characteristic of dermatitis.

Although much has been published within the last 25 years about the effect of ultraviolet light and visible light on human tissues, a precise description of the way in which human skin reacts to this type of radiation is not yet available.

The Structure of the Skin

The skin is divided into two main layers, epidermis and dermis. The epidermis is again divided into superficial and deep layers.

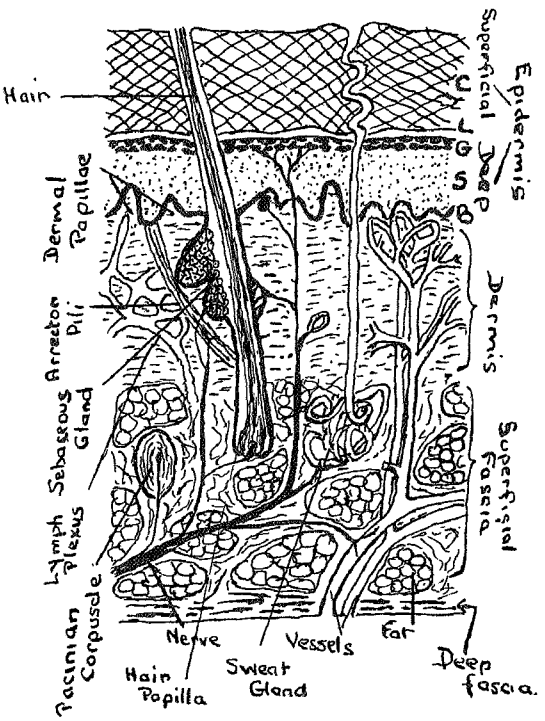

FIGURE 1

Section of thick skin, superficial fascia and deep fascia. C = stratum corneum; L = stratum lucidum; G = stratum granulosum; S = stratum mucosum, Malpighian or prickle cell layer; B = stratum germinativum (after Appleton, Hamilton and Tchaperoff).

The deep layer of the epidermis is also composed of two layers, the basal layer resting on the papillae of the dermis is called the stratum germinativum and is the reproductive layer. Pigment is formed in the deep epidermis. The more superficial layer of the deep epidermis is the stratum mucosum, or Malpighian layer, a mass of irregular nucleated cells (prickle cells).

The superficial epidermis is composed of three layers:

(a) Stratum granulosum;
(b) Stratum lucidum;
(c) Stratum corneum.

Blisters following ultraviolet irradiation form between the strata granulosum and lucidum.

To complete this brief revisory picture, the dermis consists mainly of fibrous tissue and projects upwards in the form of papillae containing capillary loops from deeper blood vessels.

The stratum corneum is the principle ultraviolet absorber, beyond this the only barrier is melanin.[13]

The Effect of Irradiation on the Skin

Sunburn is thought to be due to the reaction of the relevant cells of the epidermis to the absorption of the rays. Absorption probably takes place in a protein molecule in three layers, which spits into two or more parts. One of the products is a vasodilatory substance which diffuses gradually into the subcutaneous layers, where it can cause dilatation of blood vessels, resulting in erythema some hours after irradiation. The production of pigment in the stratum germinativum is stimulated and this is eventually apparent as a suntan. The delay between irradiation and erythema is attributed to the time taken for the activated molecule to diffuse to the capillaries.

Normal skin reaction to exposure to sunlight and ultraviolet light produces three main responses:[3, 4]

(i) Erythema;
(ii) Melanization if exposure is of a sufficent degree;
(iii) Hyperplasia or thickening.

The latter two are protective in nature.

(i) Erythema or redness of the skin appears from 2-24 hours later. It varies in degree, time of onset and duration owing to many factors which include:
  (a) Duration of exposure;
  (b) Time of day;
  (c) Season of year;
  (d) Altitude;
  (e) Amount of ozone, water vapour or smoke and dust in the air;
  (f) Reflectance from ground substances or the skin;[6]
  (g) "Sky-radiations" caused by scattering of the ultra violet radiations, the shorter wavelengths being scattered more strongly. It is these radiations which can cause an erythema reaction of the skin of a sun-bather even protected by an umbrella.[27] Haze and fog increase the scattering and, therefore, this radiation.

  The erythema is due to dilatation of minute vessels in the exposed area accompanied by swelling, often very slight but if the exposure is prolonged, the oedema is marked and blisters and desquamation may follow, accompanied by pain and itching. The erythema fades after a few days.

(ii) Melanization includes three physiological processes:
  (a) Production of new melanin granules in the melanocytes present in the basal layer of the epidermis.
  (b) Outward migration of pigmented cells and melanin granules.
  (c) Oxidative darkening of performed pale melanin.[8]

  Ultraviolet rays beyond the erythema range produce this result which occurs immediately and can occur through glass.

  Melanin absorbs some erythema producing radiation.

(iii) Hyperplasia or Hyperkeratosis.[5] There is an active proliferation and thickening of the epidermis, which occurs mainly in the horny layer and

is thought to be the main protection against ultraviolet light penetration. This is because the stratum corneum or horny layer absorbs ultraviolet light and flattened horny and granular layers reflect and scatter light so preventing the rays reaching deeper, easily damaged skin layers.

Electromagnetic Spectrum

A reference to the Electromagnetic Spectrum will be made at this point to clarify the parts of the Spectrum responsible for the problem under discussion.[6, 9, 10, 11, 12]

(a) Wireless waves — Kilometers → 1,000,000 A°
(b) Infrared rays — 4,000,000 A° → 7,700 A°
(c) Visible rays — 7,700 A° → 3,900 A°
(d) Ultraviolet rays — 3,900 A° → 1,800 A°
(e) X-rays — 1,019 A° → 0.06 A°
(f) Gamma rays — up to 1.4 A°

Sunlight spectrum 20,000 A° → 2,900 A°

Erythema spectrum in two main bands 2,540 A° → 3,650 A° generally accepted to be
(i) 2,540 A°
(ii) 2,970 A°

Melanization spectrum
— ultraviolet light 2,900 A° → 3,900 A°
— visible light 3,900 A° → 6,500 A°

Carcinogenic wavelengths are believed to be 2,850 A° → 3,300 A°

The Kromayer lamp with which the experiments to be described were done — 6,000 A° → 1849 A°

Pure infrared as used in the experiment 150,000 A° → 7,700 A°

Photosensitizers

1. *Skin applications*

Dyes: Eosin, fluorescein, Methylene blue, Rose Bengal and acriflavine.[14]

Perfumes: Oil of Bergamot, berloque and shalimar perfume and oil of citron.

Plants: Meadow grass, fig, parsnip, celery and buttercups.

Oral agents

Porphyrins and other light sensitizing agents which may reach the skin from the digestive tract.

Drugs:

Phenothiazines
Tolbutamide and other hypoglycaemics
Tetracycline
Phenergan
Quinine
Arsenical drugs
Sulphonamides
Diuril and other anti-hypersensitive agents
Griseofulvin with its fungistatic effect
Methoxsalen, used in the treatment of vitiligo because of its photosensitizing properties.

3. Injections

Gold
Tetracycline.

EFFECT AND MECHANISM OF PHOTOSENSITIVITY

As previously stated there is a difference between the two abnormal reactions to light.

Phototoxic Reaction

There are two essentials:

(a) a photosensitizer located in the epidermis (usually in the stratum mucosum or prickle cell layer) in the required concentration;
(b) exposure to the wavelength of light contained in its absorption spectrum.

Reaction follows with erythema which persists for several days and leaves hyperpigmentation. If the quantity of both essentials is great enough, blistering will occur.

Photoallergic Reaction

If a sunburn reaction plus a second delayed reaction occurs after an incubation period of several days, it is photoallergy. The reaction is urticarial, papular or eczematous with no residual hyperpigmentation. On retesting, the reaction time is shortened to minutes or hours and local testing by light may flare up previously diseased distant areas.

An erythema in this reaction seems to be the important precipitating factor and, at times an intense erythema is required.

There is much speculation as to the mechanism of this reaction, but as the actual mechanism of normal reaction to irradiation is unknown, a hypothesis is the best answer at the moment. The most reasonable one assumes that light changes a substance which normally is present in human skin, a pro-antigen into an antigen or, more important, it makes a chemical, such as a drug present in the skin, antigenic and then, in susceptible individuals, antibodies are produced and so an allergic reaction takes place.

Therefore ultraviolet absorbing chemicals such as sulfonilimides and oil of bergamot can produce both phototoxic and photo allergic relations; phototoxic potentially in all and photoallergic in the few susceptible individuals.

Other mechanisms may be involved, one being a concept of biological inhomogeneity[1] —that is that people differ in biological constitutions and do not react in the same way to drugs ingested. Complete knowledge of the metabolic fate of drugs ingested and the method by which they are eliminated from the body may lead to the discovery of various enzyme deficiencies or genetic traits. Changes are not localized to the skin alone but the gastrointestinal tract and other organs by the administration of antibiotics. Certain organisms are inhibited while others are then allowed to grow more freely. An ecologic disturbance is thus created: for example it has been recently stated that tetracycline drugs interfere with the metabolism of the vitamin B group leading to the production of pellagra-like conditions with an increase of porphyrins in the urine. This is also considered true of the barbiturates and sulphonamides. The same mechanism pertains to porphyrins, porphyria and drugs which produce porphyrinurea, because of altered porphyrin metabolism.

There are several specific conditions in which photo-sensitivity may be significant. These include:

Porphyria;

Pellagra;

Herpex simplex;

Lupus erythematosus;

Solar urticaria and polymorphic light eruptions.

Porphyria is a metabolic disturbance.[2] There are two types:

(i) congenital;

(ii) hepatic.

The congenital form only has photosensitivity as a manifestation.[21] The characteristics are:

(i) Red urine from birth because of the presence of excessive porphyrins.

(ii) Teeth and bones stained pink.

(iii) Photosensitivity with urticarial lesions, erythematous papules and visicles on face and ears and uncovered portions of arms and legs.[4] The theory assumes that the lesions are due to the presence of photosensitive porphyrins in the skin.[5] The main causative light band is 4,050 A°.

Pellagra is due to deficiency in nicotinic acid, one of the Vitamin B complex, and may occur in recluses, alcoholics, elderly widowers on improper diet or with psychiatric disorders. The diagnostic triad is dermatitis, diarrhoea and dementia. Photosensitivity is common in exposed areas with scaling and marked fissuring and follicular hyperkeratosis on the face. Nervous symptoms occur commencing with fatigue, insomnia, headaches and vertigo. Alimentary tract affections are also present.[5, 21]

Lupis Erythematosus is a systematic disease which may be acute or subacute. The lesions located on exposed areas are described as slightly infiltrated patches of persistent erythema covered with scales. The disease is one subject to severe exacerbations.[22]

Solar Urticaria and other polymorphic light eruptions are the commonest manifestations of light sensitivity and can be plaque like, contact eczematous, papular and itching or erythematous eruptions. They usually occur in spring and summer and disappear in autumn and winter. Sunlight is stated to be the cause

and to aggravate the conditions. The etiology is obscure, and is due, probably, to some allergic mechanism.

Herpex Simplex or Labialis is commonly exhibited as a bunch of vesicles on lips and nostrils precipitated by exposure to sunlight, though not always so. The mechanism is obscure.

Contact Photodermatitis is a condition in which a substance applied externally to the skin causes hypersensitivity to light. Known photo contacts include perfume oils, oil of citrus fruits (especially limes), coal tar and other plant oils.[16]

MANAGEMENT OF THE PHOTOSENSITIVE REACTION

(1) Adequate explanation of the condition to the patient with instructions to avoid exposure and protect the exposed areas if this is possible.

(2) Either to discontinue using or taking the photosensitizing agent or, if it is necessary to take the drug, to avoid exposure.

(3) In solar urticaria, the antihistamines are used with effect.[20]

(4) Anti-malarial drugs are used to protect the skin particularly with lupus erythematosus. As these patients with skin manifestations are prone to develop squamous and basal cell carcinomata, the use of chloroquine has been tried to reduce the formation of new lesions but the side effect, namely retinal damage with prolonged use, is irreversible. The mechanism by which these drugs work is unknown. Atebrine absorbs light rays from 2,500 A° → 3,000 A° and chloroquine from 3,100 A° → 3,500 A°. An interesting sidelight on the use of atebrine, was an observation by a fellow physiotherapist. He had a very fair skin and burnt very easily in the summer. After six months on atebrine (prophylaxis against malaria) in New Guinea during the war, he has no longer had to be careful with exposure in the summer time.[1, 4, 18, 19, 25]

It has been strongly suggested that drug manufacturers be required to add photosensitivity property tests to other standard procedures before releasing drugs for sale.[17]

(5) Provision of chemical "sun screens" to absorb the ultraviolet light.

(6) Application of opaque "sun shade" to scatter the light rays.

The use of sun screens needs some elaboration because the physiotherapist's assistance is often required during this part of the treatment.

It is necessary to ascertain:—

(a) the individual's degree of intolerance;
(b) the wavelength producing the abnormal action;
(c) the most effective sun screening agent.

The causative or action spectrum (the band of wavelengths which, striking the skin, cause the reaction) is determined.

Most of the reactions are caused by the erythema spectrum 2,750 → 3,200 A°, so after a test dose to estimate the patient's reaction to the particular lamp being used, filters are used in further tests to isolate the causative wavebands. These selectively absorb some rays and allow others through.

The main filters used[9, 23] are:

(i) Window glass which absorbs rays below 3,300 A° and requires six times the first degree erythema exposure to produce the same result.

(ii) Vita glass which absorbs rays below 2,750 A°.

(iii) Blue uviol absorbs abiotic rays below 2,900 A° and requires four times the first degree erythema exposure.

(iv) Wood's filter, oxide of nickel glass, and Chance's ultraviolet glass which transmit ultraviolet rays only.

(v) Cellophane, one thickness 0.06 mm. absorbs below 2,700 A° together with paraffin and cod liver oil which also absorb the shorter rays of ultraviolet light.

Once the action spectrum is determined some screen with a selective absorption is used as a topical application. To check its efficiency the test dose is repeated using ten times the first degree erythema reaction.[24]

The absorption spectra of the following are known to be in the erythema range of the spectrum though some absorb the longer wavelengths as well.

Chemical sunscreens include:

(1) Para aminobenzoic acid (PABA) 15% in hydrophilic ointment is most commonly used as it absorbs rays up to 3,200 A°. This can be given for ingestion as sodium para aminobenzoic acid.[24]

(2) Yellow petrolatum.

(3) Diachylon onintment.

(4) Phenyl salicylate 10%.

The opaque "sun shades", which scatter the light so that they never reach the light reactive part of the skin, include:

(1) Bentonite.

(2) Zinc oxide.

(3) Calamine.

(4) Ointments containing quinine or chloroquine.[15]

(5) Titanium dioxide which is in powder form and absorbs 2,900 A° → 3,900 A°.

Dark red petrolatum which was supplied for use on rafts in planes and ships in World War II and is a most effective agent against sunburn because of its adherence but is greasy, messy and difficult for the patient to remove.

Some preparations contain both "sun shade" and "sun screen" agents. It should be noted that these cause heat stasis and hinder perspiration and may result in prickly heat.

Spectrophotometry is used to determine the absorption spectrum of the "sunscreening" compound to be used.[25] Usually the Physics Department provides the machine used and the information required.

A good "sun screen" should be stable in the presence of the erythemogenic wavelengths, non-volatile, non-toxic, non-irritative nor sensitizing. The preparations must be reapplied depending on the amount of sweat and the use of water. They are usually effective 1-2 hours on exposure equivalent to noonday sun.

Physical screens are provided by closely woven brown, orange or red fabric.

DANGERS ASSOCIATED WITH ULTRAVIOLET AND SUNLIGHT EXPOSURE

It is insufficiently recognized that sunlight is not a benign physical agent.[5] One should be aware of its untoward effects especially under certain circumstances.

It is pointed out that, for instance, photosensitizers accentuate the effects of seemingly mild or normal harmless light exposure.[16] Long waves of ultraviolet light (3,200 A° → 4,200 A°) which are biologically inactive were proved harmful associated with a photosensitizer.

New dermographical data has demonstrated without doubt that exposure to sunlight is an important cause of basal and squamous cell carcinomata found in exposed skin.[5] The incidence is higher in light skinned people.

Considering the cosmetic aspect of sun exposure, one finds that irradiation ages the skin prematurely, causing collagen degeneration which is independent of age, being determined by the amount of injury from ultraviolet irradiation.[8, 5] This is accompanied by coarsening of the skin texture and spotted hyperpigmentation with the lips appearing scaly, fissured and thickened. The hair bleaches, becomes brittle and its condition is difficult to restore.

Freeman[14] working with guinea pigs reported that after injection of eight methoxypsoralen (which absorbs ultraviolet spectrum 2,200 A° → 3,500 A°) followed by exposure to ultraviolet light, liver damage occurred together with reaction in the conjunctiva cornea, iris and subcapsular epithelium. There is evidence that comparable effects occur in man by photosensitizing agents, particularly drugs.

Ultraviolet wavelengths causing sunburn cause injury to the cells of the cornea and conjunctiva leading to photophthalmia (that is pain, visual disturbances and photophobia, also with excessive secretion, oedema and purulent discharge).[7] This is "sunburn" of the eyes and does not confer protection against subsequent exposure. If occurs in arc welders as well as in "snow and glacier" blindness.

Protection, as well as periodic medical checks, is therefore important, particularly for outdoor workers.

It is interesting to note that in a survey done by the American Medical Association Chemical Laboratory, 56 suntain creams, lotions and oils were tested.[8] Thirty did not have an active protective ingredient and one had an insect repellant as an active ingredient. Para aminobenzoates and salicylates were most commonly found as active ingredients and they found that para aminobenzoic acid 2% and tannic acid were the best screening agents. Some preparations caused allergic dermatitis immediately or after weeks or months (the active ingredient usually being the cause).

The magazine "Choice" carried out and published a similar survey of local products.[26]

THE EFFECTS OF ULTRAVIOLET LIGHT EXPOSURE WITH THREE DIFFERENT AGENTS

The following experiment was undertaken to determine the effects of ultraviolet light exposure with three different agents, dithranol .2% in yellow paraffin, infrared rays and salt water 2.7% solution (equivalent to sea water).

The dithranol ointment is used on patients with psoriasis to act as a sensitizer before ultra violet irradiation.

It is claimed that giving infra red before the application of ultraviolet will enhance the effect but that given after ultraviolet irradiation will reduce the reaction.

From personal experience, salt water appeared to increase the erythema reaction.

Technique

(a) The skin on the lower abdomen, not previously exposed to sunlight, was cleaned with methylated spirits as it is an accepted fact that wavelengths below 3,300 A° can be absorbed by the urocanic acid in perspiration.[6, 15]

(b) Six students were used as subjects and their first degree erythema in contact with the Kromayer was estimated.

(c) The results were recorded, the average first degree erythema being $\frac{3}{4}$ second in contact.

(d) To estimate suitable times for photography the students were given an estimated third degree erythema and it was found that these showed up within 4 hours, therefore it was decided to film results at 2, 4 and 6 hours.

(e) The five areas on the skin were marked with a skin pencil, using an unexposed area again, the upper part of the buttocks.

Circle 1 was given infrared before ultraviolet irradiation;

Circle 2 had dithranol .2% applied to it;

Circle 3 was the control;

Circle 4 had salt water applied to it (1 teaspoon to $4\frac{1}{2}$ ounces to give a 2.7-2.8% solution);

Circle 5 had infrared after ultraviolet irradiation.

A screen of insulwool was used to isolate circles 1 and 5 at the appropriate times.

(a) The skin was cleaned with methylated spirits and the five circles drawn on.

(b) Circle 1 was given infrared for 15 minutes, producing a good localized erythema.

(c) Dithranol and salt water were applied to circles 2 and 4 respectively and all the circles were given 4 seconds in contact with a "Kromayer" lamp (water cooled hot quartz mercury vapour lamp).

(d) Circle 5 was given infrared for 15 minutes after this. It was interesting to note that each student felt this warmth more acutely following the ultraviolet irradiation.

(e) Photographs were taken at two and four hours with three of the students, and two and six hours with three of the students.

RESULTS

Grade I = Reactions less than the control.

Grade II = Control or estimated E3 reaction.

Grade III = Reactions greater than the control.

(1) Infrared before ultraviolet irradiation:

Grade III — 3 students.

Grade II — 2 students.

Grade I — 1 student.

(2) Dithranol .2% ointment:
Grade I — 1 student.
No reaction— 5 students.

(3) Salt water:
Grade III — 1 student.
Grade II — 1 student.
Grade I — 4 students.

(4) Infrared after ultraviolet irradiation:
Grade III — 1 student.
Grade I — 4 students.
No reaction — 1 student.

The number of students used was too small to draw any definite conclusions, but the results would appear to suggest that:

(1) Infrared given before ultraviolet does act as a sensitizer.

(2) That dithranol is not a sensitizer.

(3) That salt water was a sensitizer with some persons.

(4) That infrared following ultraviolet does, in most cases, act as a desensitizer.

SUMMARY

1. Photosensitivity and photosentitizers were defined, their results discussed together with their mechanisms.

2. Specific conditions were briefly mentioned in which photosensitivity plays a part.

3. Management of the photosensitivity problem was given.

4. An experiment was described which indicated that infrared irradiation prior to that of ultraviolet light, acted as a sensitizer, but given after ultraviolet light acted as a desensitizer. Salt water could be a sensitizer with some persons and that dithranol was not a sensitizer but rather the reverse.

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